Risk Factors for Persistent Carriage of Methicillin-Resistant *Staphylococcus aureus*

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We determined risk factors associated with persistent carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) among 102 patients enrolled in a double-blind, placebo-controlled trial of nasally administered mupirocin ointment. MRSA decolonization was unsuccessful in 77 (79%) of 98 patients who met the criteria for evaluation. By univariate analysis, 4 variables were found to be associated with persistent MRSA colonization ($P < .1$ for all 4): absence of mupirocin treatment, previous fluoroquinolone therapy, ⩾2 MRSA-positive body sites, and low-level mupirocin resistance. After multivariable Cox proportional hazards modeling, the presence of ⩾2 positive body sites (adjusted hazard ratio [AHR], 1.7; 95% confidence interval [CI], 1.0–2.9) and previous receipt of a fluoroquinolone (AHR, 1.8; 95% CI, 1.0–3.3) were independently associated with MRSA persistence, whereas nasal mupirocin tended to confer protection (AHR, 0.6; 95% CI, 0.4–1.0). Low-level mupirocin resistance was observed in 9 genotypically different MRSA strains and was not independently associated with chronic MRSA carriage (AHR, 1.5; 95% CI, 0.9–2.5). Our findings suggest that multisite MRSA carriage and previous receipt of a fluoroquinolone are independent risk factors for persistent MRSA colonization.

Mupirocin ointment was introduced in the United Kingdom in the mid-1980s and has subsequently been demonstrated to be highly effective in the eradication of nasal carriage of both methicillin-sensitive and methicillin-resistant strains of *Staphylococcus aureus* [1]. However, reports of mupirocin-resistant strains of staphylococci have continued to appear since they were first described in 1987 [2]. Usage patterns that have promoted the emergence of mupirocin resistance include application of mupirocin ointment for long periods of time and its indiscriminate use within an institution [1]. The general consensus is that high-level resistant strains (MIC, >256 μg/mL) cannot be eradicated with mupirocin, whereas the clinical significance of low-level mupirocin resistance (LMR) remains dubious [3, 4].

We recently reported the results of a double-blind, placebo-controlled trial that demonstrated the failure of nasal mupirocin ointment to eliminate multisite carriage of methicillin-resistant *S. aureus* (MRSA) [5]. Surprisingly, by unadjusted statistical analysis, we observed a significant association between LMR and subsequent treatment failure in patients in both study arms. In the present analysis, we determined independent risk factors associated with persistent MRSA carriage and further assessed the significance of LMR, adjusted for confounding variables.

Methods

A complete description of the patients and methods has been reported elsewhere [5]. In brief, from October 1995 through September 1997, 102 patients with MRSA carriage and without signs of active infection were randomly assigned to receive either placebo (51 patients) or nasally applied mupirocin (51 patients) for MRSA eradication. All patients received daily baths or showers with 4% chlorhexidine soap (Hibiscrub; Zeneca Pharma, Cergy, France) for whole-body washing, that included the hair and the perianal region. At baseline, 55% of patients had MRSA colonization simultaneously at different body sites. The primary study end point was the efficacy of nasally applied mupirocin in the eradication of MRSA carriage at any body site. Failure was defined as the recovery of a positive MRSA culture result from any body site within 1 month after randomization [5].

Possible predictors of persistent MRSA carriage explored in the present analysis were as follows: age, sex, underlying diseases and comorbidities, nutritional and functional status, device exposure (urinary catheters, central venous catheters, or both), antibiotic exposure during the present admission, previous MRSA history, colonization site, number of positive sites, transfer from another hospital or long-term care facility, presence or absence of exposure to mupirocin in the study, mupirocin resistance, and infection of control measures such as contact isolation. Each patient was assessed for the presence

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of the following underlying conditions: coronary heart disease (resulting in permanent alteration of the cardiac function [New York Heart Association classes III or IV]), diabetes mellitus (requiring either oral therapy or insulin treatment), pulmonary disease (resulting in functional disability and/or requiring chronic bronchodilator therapy), gastrointestinal disease (e.g., hepatitis or gastroduodenal ulcers), renal disease (chronic underlying renal disorder), cancer (malignant disease process causing permanent disability), and neurologic disease (stroke or other active neurologic conditions with permanent disability). In addition, we classified the patients' functional status as belonging to 1 of 3 categories: (1) requires minimal assistance in performing activities of daily living; (2) requires moderate, occasional assistance and has sporadic bladder incontinence; and (3) requires heavy, permanent assistance to perform activities of daily living and has chronic incontinence of the bladder and the bowel.

Antimicrobial susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards [6], by use of disk diffusion methodology. The zone diameter breakpoints for both isolates susceptible to mupirocin and isolates resistant to mupirocin were $\geq$14 and $\leq$13 mm, respectively [7]. In addition, MICs of mupirocin were determined by E test methodology (AB Biodisk, Solna, Sweden). The MIC breakpoints for mupirocin were $\leq$4 mg/L for susceptible isolates, 8–64 mg/L for isolates with low-level resistance, 128–256 mg/L for isolates with intermediate-level resistance, and $\geq$500 mg/L for isolates with high level resistance [8]. *S. aureus* ATCC 29223 was used as a quality control strain for disk diffusion testing and determination of MICs. Molecular typing of MRSA isolates was performed by means of contour-clamped homogenous electric-field electrophoresis [9].

We expressed continuous variables as the mean ($\pm$ SD) or as the median and interquartile range if their distribution was skewed. Baseline characteristics were compared by use of the Student's t test or Wilcoxon test, for continuous variables, and by use of the χ^2 test or Fisher's exact test for assessment of differences in proportions.

For all patients meeting the criteria for evaluation, observation continued from randomization for at least 30 days, or until treatment failure or loss to follow-up, if either occurred in the interim. Kaplan-Meier failure curves were drawn and compared between different groups by use of the log-rank test; we counted patients who were positive with MRSA after randomization as having treatment failures, and the remainder were considered censored as of the last day of observation. We looked for independent risk factors of persistent MRSA carriage by use of a stepwise Cox proportional hazards model [10]. This model assessed the effect of each predictor on the hazard rate of failure over time, after adjustment for other factors and after allowing for censoring because of discharge, death, or loss to follow-up [11]. We used graphical methods to check the proportional hazards assumption and searched for effect modification by including appropriate interaction terms [12]. All continuous variables were categorized or dichotomized because none of them satisfied the linearity assumption. Variables for which P was $<.15$ were entered into the multivariable analysis. Confounding was tested by examination of effect sizes (β coefficients) with and without inclusion of the potential confounder in the model [13]. Variables that caused substantial confounding (change in β coefficients, $\geq$20%) were included in the final model. The strength of the association between prognostic variables and the outcome of interest was expressed as a hazard ratio (HR), and the corresponding 95% CIs were calculated.

To identify risk factors predicting MRSA recolonization after the end of the chlorhexidine baths or showers, we further divided follow-up into 2 periods. For the late period, a Cox proportional hazards model was created with all observations starting on day 10 (the end of chlorhexidine body washing); it excluded all patients having a time to MRSA detection of $\leq$9 days.

All statistical tests were 2-tailed. $P < .05$ was considered significant. Statistical packages used were SPSS, version 8.0 (SPSS, Chicago) and Stata, version 6.0 (Stata, College Station, TX).

Results

Of the 102 patients enrolled in the study, 4 were excluded (because of major protocol violations in the first 24 h); therefore, at the time of randomization, there were 98 patients who

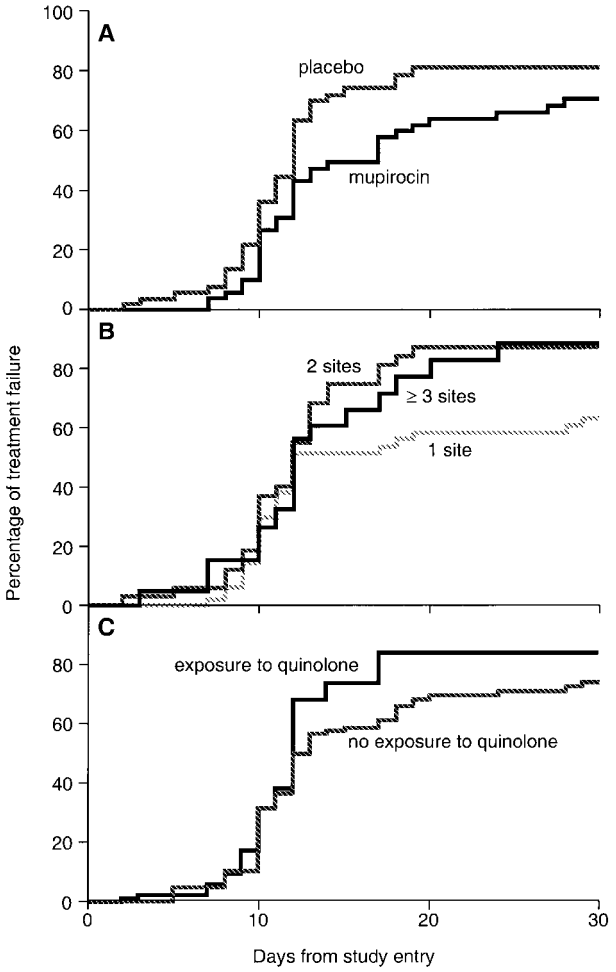

Figure 1. Kaplan-Meier probability estimates for the 30-day failure rate of all patients (n = 98) according to *(A)* treatment assignment; *(B)* the number of methicillin-resistant *Staphylococcus aureus* carriage sites at baseline; and *(C)* fluoroquinolone exposure before study enrollment.

were only colonized with MRSA and who met the criteria for evaluation. Of these patients, 77 (79%) had persistent MRSA carriage at the end of follow-up. Important characteristics of patients with and without treatment failure are summarized in table 1.

As shown in figure 1*A*, the probability of MRSA persistence 30 days after randomization was 0.75 for the patients in the mupirocin-treated group and 0.82 for the patients in the placebo-treated group (by log-rank test; $P = .097$). The median interval to failure was 12 days (95% CI, 11–13 days) for the placebo group and 14 days (95% CI, 9–19 days) for the mupirocin group. Figure 1*B* displays the Kaplan-Meier curves according to the number of MRSA carriage sites at baseline.

By univariate Cox regression analysis, we found that 4 variables were associated with persistent MRSA carriage ($P < .1$ for all 4; table 2): previous fluoroquinolone therapy (HR, 1.6; 95% CI, 0.9–2.7; figure 1*C*), ⩾2 body sites positive for MRSA (HR, 1.8; 95% CI, 1.1–2.9), absence of mupirocin treatment (HR, 1.5; 95% CI, 1.0–2.3), and LMR (HR, 1.6; 95% CI, 1.0–2.6). After adjustment for confounding variables (urinary tract carriage and mupirocin treatment before study entry), the presence of ⩾2 body sites positive for MRSA (adjusted HR [AHR], 1.7; 95% CI, 1.0–2.9; $P = .035$) and previous receipt of a fluoroquinolone (AHR, 1.8; 95% CI, 1.0–3.3; $P = .048$) were independently associated with MRSA persistence, whereas treatment with nasal mupirocin tended to confer protection (AHR, 0.6; 95% CI, 0.4–1.0; $P = .066$; table 3). Although we observed differing probabilities of cumulative failure (figure 2)

Table 1. Comparison of patients with and without persistent carriage of methicillin-resistant *Staphylococcus aureus* (MRSA).

Characteristic	Patients with persistent MRSA ($n = 77$)	Patients without persistent MRSA ($n = 21$)	*P*
Female sex	36 (47)	4 (19)	.02
Mean age ± SD, y	75.7 ± 13.9	67.5 ± 20.1	.09
Mean weight ± SD, kg	67.6 ± 19.3	69.9 ± 17.3	.6
Previous hospitalizations, mean ± SD	6.7 ± 5.7	3.5 ± 5.3	.2
Direct admission from home	45 (58)	10 (48)	.4
Comorbidities, mean ± SD	3.3 ± 2.1	3.5 ± 2.0	.7
Underlying conditions			
Coronary heart disease	19 (25)	5 (24)	1
Diabetes mellitus	25 (32)	7 (33)	1
Pulmonary disease	18 (23)	6 (29)	.6
Gastrointestinal disease	16 (21)	6 (29)	.4
Neurologic disease	26 (34)	5 (24)	.2
Renal disease	11 (14)	2 (10)	.7
Cancer	9 (12)	3 (14)	1
Functional status			
Minimal assistance required	42 (55)	9 (43)	.3
Moderate assistance required	14 (18)	3 (14)	1
Permanent assistance required	21 (27)	9 (43)	.2
Supplemental enteral nutrition	12 (16)	5 (24)	.5
Duration of known MRSA carriage, median (interquartile range), d	11 (180)	35 (379)	.7
Previous mupirocin exposure	18 (23)	4 (19)	.7
Contact isolation	69 (90)	19 (90)	1
Urinary catheter	20 (26)	5 (24)	.8
Central venous catheter	8 (10)	3 (14)	.7
Mupirocin study exposure	36 (47)	12 (57)	.4
Any previous antibiotic exposure during the present admission	31 (40)	11 (52)	.3
Recent receipt of fluoroquinolones[a]	19 (25)	0 (0)	.006
Low-level mupirocin resistance at the end of treatment	24 (31)	0 (0)	.001
Colonized body sites at baseline			.04
1	30 (39)	14 (67)	
2	25 (32)	5 (24)	
⩾3	22 (29)	2 (9)	
Number of colonized sites, mean ± SD	1.90 ± 0.82	1.41 ± 0.67	.01
Nasal carriage	48 (62)	9 (43)	.1
Groin/perianal carriage	31 (40)	6 (29)	.3
Skin carriage other than groin/perianal	38 (49)	11 (52)	.8
Urinary tract colonization	16 (21)	4 (19)	.9

NOTE. Data are no. (%) unless otherwise indicated.

[a] During the present admission before inclusion in the study. Ciprofloxacin, 14 patients; norfloxacin, 5 patients.

Table 2. Simple Cox regression analysis indicating risk factors for persistence of methicillin-resistant *Staphylococcus aureus* (MRSA).

Variable	*n*	Persistent MRSA carriage, *n* (%)	Hazard ratio	95% CI	*P*
Demographic characteristics					
Female sex	40	36 (90)	1.31	0.83–2.05	.29
Age >75 y	53	42 (79)	1.04	0.66–1.63	.86
Previous hospitalization	77	66 (86)	1.20	0.63–2.28	.57
Underlying conditions and health status					
Coronary heart disease	24	19 (79)	1.11	0.66–1.87	.69
Diabetes mellitus	32	25 (78)	1.12	0.62–2.05	.73
Pulmonary disease	24	18 (75)	0.88	0.49–1.57	.69
Neurologic disease	31	26 (84)	0.98	0.61–1.58	.96
Gastrointestinal disease	22	16 (73)	1.05	0.70–1.58	.79
Cancer	12	9 (75)	1.02	0.51–2.04	.90
>3 comorbidities	42	31 (74)	0.78	0.49–1.23	.38
Bad functional status requiring permanent assistance	30	21 (70)	0.82	0.50–1.34	.43
Supplemental enteral nutrition	17	12 (71)	0.75	0.41–1.41	.38
Clinical characteristics					
Newly discovered MRSA status (<2 weeks)	50	42 (84)	1.38	0.88–2.17	.16
Exposure to nasal mupirocin during another previous hospitalization	22	18 (82)	0.79	0.46–1.34	.38
Mupirocin study exposure	48	36 (75)	0.67	0.43–1.05	.08
Low-level mupirocin resistance	24	24 (100)	1.59	0.95–2.59	.08
Previous exposure to any antibiotic agent during the present admission	42	31 (74)	0.86	0.55–1.35	.51
Recent receipt of fluoroquinolones	19	19 (100)	1.57	0.93–2.66	.09
Contact isolation	88	69 (78)	1.05	0.52–2.12	.83
Urinary catheter	25	20 (80)	1.07	0.64–1.79	.68
Central venous catheter	11	8 (73)	0.70	0.36–1.46	.34
Microbiologic characteristics					
⩾2 distinct colonized body sites	54	47 (87)	1.80	1.13–2.88	.01
Nasal carriage	57	48 (84)	1.42	0.88–2.28	.16
Groin/perianal carriage	37	31 (84)	1.31	0.82–2.08	.27
Skin site carriage other than groin/perianal	49	38 (78)	0.89	0.57–1.40	.75
Urinary tract carriage	20	16 (80)	1.09	0.64–1.88	.75

for mupirocin-treated patients with and without LMR strains (log-rank test, $P = .08$), LMR was not independently associated with treatment failure in the multivariate model (AHR, 1.5; 95% CI, 0.9–2.5; $P = .15$).

In addition, we examined risk factors for late failure, considering 2 distinct periods (see the "Methods" section). The prognostic significance of previous fluoroquinolone therapy (AHR, 2.4; 95% CI, 1.2–4.6; $P = .009$) and multiple body sites positive for MRSA at study entry (AHR, 1.9; 95% CI, 1.1–3.3; $P = .026$) appeared to be more pronounced late in the follow-up. Moreover, urinary tract carriage of MRSA (AHR, 2.2; 95% CI, 1.0–4.6; $P = .041$) and LMR (AHR, 1.8; 95% CI, 1.0–3.3; $P = .045$) became independent risk factors in this model.

A total of 42 patients (43%) had received 79 different antibiotic agents during the present admission before they entered the study. Fluoroquinolones were prescribed for 19 patients (ciprofloxacin, for 14, and norfloxacin, for 5); amoxicillin–clavulanic acid, for 15; imipenem, for 11; cephalosporins, for 8; glycopeptides, for 7; clindamycin, for 5; trimethoprim-sulfamethoxazole, for 5; and other agents, for 9. No association was found between previous antibiotic exposure and persistent MRSA carriage with the exception of recent fluoroquinolone therapy, which was prescribed for a median of 7 days (range, 2–34 days). Susceptibility analysis of MRSA isolates from patients previously exposed to fluoroquinolones revealed resistance to this class of antibiotic agents in all cases.

Overall, 46 MRSA isolates with LMR were observed among 27 patients. MICs of mupirocin were as follows: for 5 isolates, 64 mg/L; for 4 isolates, 48 mg/L; for 5 isolates, 32 mg/L; for 11 isolates, 24 mg/L; and for 21 isolates, 16 mg/L. No isolate showed high-level resistance to mupirocin. At the time of study enrollment, low-level resistant strains were documented in 23

Table 3. Multivariable Cox regression model showing independent factors associated with persistent methicillin-resistant *Staphylococcus aureus* (MRSA) carriage.

Variable	Adjusted hazards ratio	95% CI	*P*
⩾2 distinct MRSA body sites	1.73	1.04–2.87	.035
Recent exposure to fluoroquinolones	1.81	1.01–3.26	.048
Absence of mupirocin therapy	1.55	0.97–2.47	.066
Low-level mupirocin resistance	1.48	0.87–2.52	.146
Urinary tract carriage[a]	1.57	0.84–2.96	.161
No previous exposure to mupirocin[a]	1.41	0.79–2.51	.251

[a] Confounding variables.

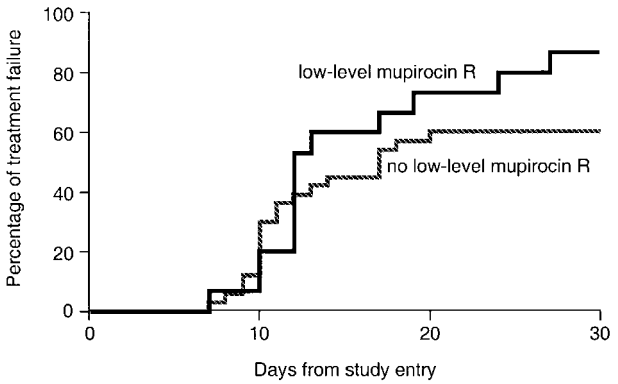

Figure 2. Kaplan-Meier curves showing the probability over time of methicillin-resistant *Staphylococcus aureus* persistence for patients only in the mupirocin-treated group ($n = 48$), stratified by the presence or absence of low-level mupirocin resistance. R, resistance.

patients. Four patients acquired low-level resistance during mupirocin therapy and 3 patients in the placebo group lost their mupirocin-resistant strains.

All 46 isolates showing LMR were available for molecular subtyping. LMR was observed in 9 genotypically distinct MRSA strains. The most frequent profile was recovered in 8 patients, followed by 2 distinct profiles, each of which involved 5 patients, and 6 other profiles that involved 1–3 patients.

Discussion

We examined risk factors for persistent MRSA carriage in 98 patients with MRSA colonization who were enrolled in a double-blind, placebo-controlled trial of nasal mupirocin. The probability of persistent MRSA colonization was almost 2 times greater among patients with >1 colonized body site and among patients who had recently received fluoroquinolones. LMR tended to increase the risk of persistent MRSA carriage, whereas nasal mupirocin treatment tended to confer protection. These findings may help explain, at least in part, the observed differences in the efficacy of topical eradication treatment in various groups of patients with MRSA carriage. More importantly, these data could help to improve existing control strategies for patients with MRSA colonization. Finally, our study results support the observation that exposure to fluoroquinolones increases MRSA adhesion and carriage, and the results further suggest that LMR may play a more important role in the failure to eradicate MRSA carriage than was previously thought.

Our discovery of a trend toward treatment failure in cases with LMR stands in contrast to the common view that LMR has no clinical impact. The latter concept is based on the finding that low-level resistant strains colonizing the nasal cavity can be eradicated with high concentrations of mupirocin and that clinical failures were only rarely observed when treating isolates demonstrating LMR [3, 4, 14]. However, no controlled study has proven this hypothesis. Anecdotally, Gaspar et al. [15] have concluded from an outbreak in Spain that MRSA colonization at multiple body sites was clinically more important than LMR in the failure of topical treatment. We confirmed this finding by performing multivariable modeling and extended it by showing that the identification of LMR was an independent risk factor for late occurrence of failure. However, a limitation of the present analysis was that the small number of LMR cases limited the precision of the calculated HRs and CIs. Therefore, we cannot confidently rule out the influence of chance alone on this worrisome finding. In addition, the evidence of a statistical association between LMR and MRSA persistence does not prove causality, although we could exclude that 1 predominant MRSA clone that biased our results. Further studies in this direction are urgently needed, but our findings should generate broader concern about the clinical significance of LMR.

The association between the administration of antibiotics and the occurrence or persistence of MRSA is complex. Although the relative participation of cross-transmission and antimicrobial selection pressure in MRSA dissemination remains to be determined, Monnet [16] recently described several lines of evidence to support the existence of an association between MRSA carriage and antimicrobial utilization. Fluoroquinolones in particular are prone to increase the occurrence and persistence of multiresistant staphylococci [16–21]. In 2 reports of MRSA outbreaks in Germany, a country with a high rate of ciprofloxacin use, thorough investigation of multiple risk factors showed that previous fluoroquinolone exposure was an independent risk factor for carriage of MRSA [18, 19]. A national surveillance study from Belgium demonstrated a direct association between MRSA occurrence and the use of fluoroquinolones [22].

Consistent biological models can explain these epidemiologic findings. Hoiby et al. [23] showed the rapid development of methicillin-resistant *Staphylococcus epidermidis* in the axilla and nostrils of volunteers receiving ciprofloxacin. Colonization by such multiresistant *S. epidermidis* strains lasted, on average, >30 days after ciprofloxacin treatment was terminated. Although these authors did not report on the findings for MRSA, ciprofloxacin is likely to have the same effect on patients carrying *S. aureus* [16, 17, 24, 25]. Finally, 2 studies performed by Bisognano et al. [26, 27] showed the increased expression of fibronectin-binding proteins by fluoroquinolone-resistant *S. aureus* exposed to subinhibitory levels of ciprofloxacin, leading to increased adhesion and prolonged carriage of *S. aureus.* Therefore, our discovery of a possible association between previous fluoroquinolone exposure and persistent MRSA colonization is consistent with other microbiological evidence and warrants confirmation in larger epidemiologic studies.

A limitation of the analysis was that the sparse data for some variables precluded a more detailed examination. For instance, only 1 patient was infected with HIV, and only 2 patients required hemodialysis. Nevertheless, the observed rate of MRSA persistence was large enough to perform valid multivariable

Cox modeling and did not compromise the accuracy and precision of the generated HRs [28].

The presented risk factor analysis offers important information about and strong quantitative estimates of the probability of persistent MRSA carriage in hospitalized patients, extending earlier findings [29]. Our data will help explain some of the disparities in reported success rates of mupirocin and other topical eradication treatments, and these insights may lead to the development of more-effective MRSA control strategies. Finally, these data highlight what type of patients may be least likely to benefit from a topical eradication regimen. Future studies that build on these results may consider new preventive strategies related to the number of carriage sites and to patients' previous exposure to fluoroquinolones, and, thus, they may be able to better target patients most likely to benefit from topical eradication therapy.

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